# Overview of the Research Program in the Division of Microbiology at NCTR

## NCTR SAB Meeting November 3-4, 2015

Carl E. Cerniglia, Ph.D., Director
**Division of Microbiology**

# The Division of Microbiology

**Mission:** To serve a multipurpose function with specialized expertise to perform fundamental and applied research in microbiology in areas of FDA's responsibility in toxicology and regulatory science.

**Vision:** Strive to be a Valued Resource in Advancing Regulatory Science Research in Microbiology for the FDA

# Achieving the Division's Vision

- **Contributing to FDA Guidelines & Regulations**
  - Integrate research program into the FDA infrastructure
  - Understand the regulatory process in order to identify issues
  - Conduct research to develop, support and enhance FDA guidelines
- **Enhancing FDA Research Interactions**
  - Conduct research critical to the FDA regulatory science mission
  - Participate and contribute to cross-Center working groups
  - Expand our collaborative relationship with FDA Centers and ORA
  - Assess the needs of FDA by working closely with NCTR's Associate Director for Regulatory Activities
- **Strengthening Research Program Management**
  - Establish benchmarks of scientific excellence
  - Focus research priorities in consultation with regulatory colleagues
  - Communicate research in plain language
  - Upgrade research facilities and infrastructure

# Microbiology Research Themes

- Evaluating interactions between human microbiome, antimicrobial agents, food contaminants, food additives, food supplements and FDA-regulated products
- Developing methods to detect and characterize foodborne and other pathogens
- Determining antimicrobial resistance and virulence mechanisms of pathogens
- Improving risk assessments of priority pollutants, including polycyclic aromatic hydrocarbons and drugs, by integrating systems biology approaches
- Conducting research to aid FDA in the areas of women's health, tobacco products and nanotechnology

# Division of Microbiology - Staff

Carl E. Cerniglia, Director

- **Government Positions (28)**
  - Principal Investigators: 18
  - Research Support Staff : 4
  - Administrative : 4
- **ORISE Post Docs, Graduate Students and Visiting Scientists:** 12
- **FDA Commissioner Fellows :** 2

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# Division of Microbiology - Staff

## Administration
Carl E. Cerniglia, Ph.D., Director
Sherry F. Terry
Paula M. Stain
Lorena Aldridge

## Research Support Staff
Joanna D. Deck
Lisa Mullis
Miseon Park
Shemedia J. Johnson

## Principal Investigators
Ashraf A. Khan, Ph.D.
Bruce D. Erickson, Ph.D.
Fatemeh Rafii, Ph.D.
Huizhong Chen, Ph.D.
Jing Han, Ph.D.
John B. Sutherland, Ph.D.
Kidon Sung, Ph.D.
Mark Hart, Ph.D.
Marli Azevedo, Ph.D.
Mohamed S. Nawaz, Ph.D.
Ohgew Kweon, Ph.D.
Rajesh Nayak, Ph.D.
Robert D. Wagner, Ph.D.
Saeed A. Khan, Ph.D.
Sangeeta Khare, Ph.D.
Seong-Jae Kim, Ph.D.
Steven L. Foley, Ph.D.
Youngbeom Ahn, Ph. D.

## ORISE
Maria Basco, Ph.D.
Dongryeoul Bae, Ph.D.
Jinshan Jin, Ph.D.
Ji Young Jung, Ph.D.
Jeong-Myeong Kim, Ph.D.
Jungwhan Chon, Ph.D.
Katherine Williams, M.S.
Kuppan Gokulan, Ph.D.
Yasser M. Sanad, DVM, Ph.D.

## Visiting Scientists/Students
Bo Jiang, Ph.D.
Haihong Hao, Ph.D.
Mohamed, Lahiani

## FDA Commissioner's Fellow
Sudhakar Agnihothram, Ph.D.
Bijay Khajanchi, Ph.D.

# Research Capabilities of the Division

## Research systems

- *In vitro* culture system
- Bioreactor -Continuous culture flow system
- *Ex vivo* system-Human intestinal tissue explant
- Animal model-gnotobiotics and humanized mice

## Research tool box

**Traditional microbiology**

- Aerobic and anaerobic bacterial culture and detection
- Gene cloning, protein expression and purification
- Fungi and viral culture and detection

**Metabolism study**

- HPLC, GC- & LC-MS, NMR analysis

**Genomics and functional genomics**

- Genome sequencing and comparative genome analysis
- Transcriptomics
- Proteomics
- Metagenomics (taxonomic and functional profiling)

# Division of Microbiology - Outreach

- **Collaborations with:**
  - All FDA Centers
  - National Toxicology Program
  - USDA, CDC
  - Universities: Local, National and International
- **Global/National Outreach:**
  - WHO Committees: JECFA
  - Science Advisory Boards
  - Journal Editorial Boards
  - US Government Panels: USDA, EPA, NOAA
  - Visiting Scientist Programs
  - FDA-wide: Expert Committees, Working groups from FDA Centers


Microbiology Research Areas
Host-Microbiome Interactions
Environmental Biotechnology
Nanotechnology
Office of Women's Health
Tobacco Products
Foodborne Pathogens & Virology
Antimicrobial Resistance

# Host-Microbiome Interactions

- Impact of antibiotic residues on the human gut microbiota
- Role of extracellular proteins in *Staphylococcus aureus* pathogenicity
- Effects of *Bacillus anthracis* on human cell lines
- Detection of microbial contaminants in tattoo inks
- Interactions of nanoparticles and the gut microbiome; tobacco products and the oral microbiome; and feminine products and vaginal microbiome

# Highlighted Accomplishment

- **Impact of antimicrobial residues on the gastrointestinal microbiota**
  - Evaluated whether the ingestion of tetracycline residues at various levels impact the human GI tract microbiota
    - Determined whether there were shifts in the microbiota populations
    - Determined the selection of antimicrobial resistant bacteria
    - Determined whether the GI bacteria degraded/inactivated the drug
  - Data supported VICH GL #36: “Studies to Evaluate the Safety of Residue of Veterinary Drugs in Human Food: General Approach to Establish a Microbiological ADI”
  - New studies being planned to evaluate the impact of erythromycin on the gastrointestinal microbiota

# Antimicrobial Resistance

- Survival of *Burkholderia cepacia* in pharmaceutical products
- Impact of antimicrobial pressure on antimicrobial resistance transmission in enteric pathogens
- Mechanisms of drug resistance in *Escherichia coli* from companion animals
- Antibiotic resistance in enteric pathogens from seafood and imported foods
- Mechanisms of fluoroquinolone resistance in *Clostridium perfringens*

# Highlighted Accomplishment

- ***Burkholderia cepacia* Complex (BCC) survival in pharmaceutical products**
  - BCC has been recovered in recent outbreaks from various pharmaceutical products
  - BCC can survive and remain viable in solutions of chlorhexidine gluconate and benzalkonium chloride for extended periods of time
  - Provided data on the susceptibility, survival and detection of BCC in pharmaceutical products containing antiseptics and the importance of proper antiseptic concentrations in pharmaceutical products

# Highlighted Accomplishment

- **Comparison of the impact of antimicrobial pressure on antimicrobial resistance plasmid transmission**
  - Antimicrobial resistant *Salmonella* donors and susceptible recipients were exposed to different concentrations of antimicrobials and the efficiency of plasmid transfer was determined
  - Results indicate that there is strain-level variability in conjugation dynamics following antimicrobial exposure
    - For multiple drug-strain combinations there was a dose-dependent impact on plasmid transfer efficiency
    - May lead to increased dissemination of antimicrobial resistance determinants

# Foodborne Pathogens & Virology

- Immune response to norovirus-bacterial co-infection
- Prevalence and epidemiology of noroviruses and coronaviruses in the US
- Virulence plasmids in *Salmonella* impacting health
  - Interplay of virulence and antibiotic resistance in *Salmonella*
- Cytolethal distending and pertussis toxin genes in *Salmonella*
- Contamination of dietary supplements with *Bacillus spp.*
- Genetic factors influencing *Campylobacter* colonization
- Microbial genetics of Shiga-toxin producing *Escherichia coli*

# Highlighted Accomplishment

- **Impact of norovirus-*Salmonella* co-infection on the immune response to the infection**
  - Norovirus infections requiring hospitalization often involve co-infection with a bacterial pathogen-*Salmonella* was most commonly detected
  - In vitro studies appear to show that *Salmonella* blocks cell death associated with norovirus infection
    - Could lead to prolonged norovirus infection and increased shedding
  - *Salmonella* numbers were also increased during co-infection
  - Ongoing work is examining the mechanism for the altered immune response during co-infection

# Tobacco Products

- Evaluation of the toxicity of smokeless tobacco on oral bacteria
- Characterization of the microbial populations of smokeless tobacco products

# Women's Health

- *Staphylococcus aureus* and the production of toxic shock syndrome toxin-1 as influenced by tampons
  - Evaluation of methods for evaluation of *S. aureus* growth and TSST-1 toxin production
- Immuno-modulatory effects of nanoparticles made of biodegradable polymers designed for drug delivery to vaginal epithelial cells and the susceptibility to *Candida* infection

# Highlighted Accomplishment

- *Staphylococcus aureus* and the production of toxic shock syndrome toxin-1 as influenced by tampons
  - Characterized the TSST-1 and alpha-toxin producing capability of clinical strains from menstrual toxic shock syndrome
  - Developed a defined medium that simulates vaginal secretions and supports the growth of *Lactobacillus* species and clinical strains o*f S. aureus*
  - Ongoing evaluation of published methods to determine that tampons do not promote the growth of *S. aureus,* increase the production of TSST-1, or alter the vaginal microbiota

# Nanotechnology

- Impact of nanoparticles on the intestinal microbiota and gut-associated immune response
- Impact of size and shape dependent-toxicity of silver nanoparticles evaluated at the gastrointestinal surface
- Understanding antimicrobial properties of zinc and titanium oxide nanoparticles and their potential impact human cells
- Effect of nanoparticle bioaccumulation in macrophages on host susceptibility to bacterial infection

# Highlighted Accomplishment

- **Evaluation of nanoparticles and their impact on changes in the microbiota and the gut-associated immune response**
  - In vitro studies demonstrated that exposure to silver nanoparticles (AgNP), especially those of smaller sizes, caused permeability changes in the intestinal epithelial barrier
  - Exposure to smaller sized AgNP also led to greater shifts in intestinal bacterial subpopulations in animal models
  - Work is ongoing to test the effects of AgNP on host response and inflammation

# Environmental Biotechnology

- Impact of crude oil residues and dispersants on human microbiota
- Systems biology approaches to elucidate the biodegradation of priority pollutants
- Identify environmental bacteria and enzymes that degrade antibiotics

# Highlighted Accomplishment

- **Bioremediation of BP Deepwater Horizon crude oil**
  - PAHs are important public health concerns as highlighted with the Deepwater Horizon oil spill and subsequent contamination
  - Utilized genomic, proteomic, metabolomic and bioinformatic approaches to determine the metabolic pathways for the degradation of polycyclic aromatic hydrocarbons (PAHs)
    - Dynamic changes were observed in protein expression of mycobacteria during BP crude oil incubation, including factors potentially involved in adaptation to crude oil

# Research on the Horizon

- Microbiome and its role in toxicological outcomes
  - Newly approved research through the National Toxicology Program
- Nanoparticles, the microbiome and the intestinal epithelium
  - Further studies of the impact of silver, titanium dioxide and graphene nanoparticles to disruption of the gut microbes and intestinal epithelia
- Development of enhanced bioinformatics approaches to analyze metagenomics data obtained from microbiome studies

# Research on the Horizon

- Fecal microbiota transplantation (FMT) and microbial biotherapeutics
  - Understanding the modulation of inflammatory responses by commensal microorganisms during C*lostridium difficile* infections and how the responses impact FMT success
- Development of a nucleic acid-based reference method for the evaluation of novel C*. difficile* diagnostic tests
- Elucidation of mechanisms underlying *S. aureus* biofilm formation on antimicrobial-coated medical devices
- Detection of mycobacterial contamination of tattoo inks

# Research on the Horizon

- Assessment of FDA regulated products and the impact of their presence in the environment on human health
  - Including antibiotics, nanoparticle and other priority pollutants
- Interplay of virulence and antimicrobial resistance in enteric pathogens
  - Development of novel approaches to evaluate plasmid genetics and establishing bioinfomatics tools to assess virulence and plasmid dynamics using whole genome sequence data
- Determination of the impact of sunlight, temperature and humidity on norovirus survival

# Future Direction of the Division

## Strategies:

- Increase the capacity and resources to conduct research to better understand the impact of FDA-regulated products on the microbiome and conversely, the impact of the microbiome on FDA-regulated products
- Advance new scientific approaches to determine the impact of chemical and microbial contaminants in foods and other FDA regulated products on the human microbiome
- Improve environmental risk safety assessments of human and veterinary drugs and priority pollutants through the integration of systems biology approaches

# Future Direction of the Division

- Continue to work with CTP to advance their research priorities to provide data directly relevant to their mission on the regulation of tobacco products
- Continue to develop nanotechnology projects in collaboration with the NCTR NanoCore Facility and FDA regulatory centers
- Build on previously funded studies in women's health to identify research gaps to address new initiatives with the Office of Women's Health
- Identify opportunities to leverage opportunities with other federal, state and international regulatory and public health agencies, academia and industry

# Future Direction of the Division

- The Division is diverse in expertise and well suited to meet the microbiological needs of FDA Centers and special programs (OWH, OCS, etc.)
  - Therefore we have worked to reach out to our stakeholders to develop research projects that help them address their needs to meet FDA's mission
- Through these interactions with the FDA Centers, we have prioritized our research efforts by moving away from areas of with less need to those more pressing to the agency
  - This flexibility is an key asset to the NCTR and FDA as a whole

# Feedback Requested

- As a Division, are we addressing the needs of the FDA Centers?
  - What emerging sciences/technologies can you advise the Division to pursue?
- How can we do a better job of engaging the Centers to learn about the needs?
- What future directions do you recommend for this division that would impact the FDA?

# Thanks a lot!!!

- Members of the Science Advisory Board
- Dr. William Slikker. Jr., Director, NCTR
- Dr. Daniel Acosta, Deputy Director, NCTR
- Dr. Donna Mendrick,  Assoc. Director for Regulatory Activities
- Division of Microbiology Staff

Food and Drug Administration
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## Contact Information:

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